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US-PAT-NO: 6187304
DOCUMENT-IDENTIFIER: US 6187304 B1

TITLE: Effects of IFN-.gamma. on cardiac hypertrophy

ODP

DATE-ISSUED: February 13, 2001

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/85.5; 435/69.51

CLAIMS:

What is claimed is:

1. A method for reducing the weight of heart in a patient diagnosed with cardiac hypertrophy, comprising administering to the patient an effective amount of interferon gamma (IFN-.gamma.).

2. The method of claim 1 wherein said patient is human.

3. The method of claim 2 wherein said IFN-.gamma. is recombinant human IFN-.gamma.(rh-IFN-.gamma.).

4. The method of claim 3 wherein said IFN-.gamma. is rhIFN-.gamma.-1b.

5. The method of claim 3 wherein said cardiac hypertrophy is characterized by the presence of an elevated level of PGF.sub.2.alpha..

6. The method of claim 2 wherein said cardiac hypertrophy has been induced by myocardial infarction.

7. The method of claim 6 wherein said IFN-.gamma. administration is initiated within 48 hours following myocardial infarction.

8. The method of claim 7 wherein said IFN-.gamma. administration is initiated within 24 hours following myocardial infarction.

9. The method of claim 2 wherein said IFN-.gamma. is administered in combination with at least one further therapeutic agent used for the treatment of cardiac hypertrophy or a heart disease resulting in cardiac hypertrophy.

10. The method of claim 9 wherein said further therapeutic agent is selected from the group consisting of a .beta.-adrenergic-blocking agent, verapamil, difedipine, and diltiazem.

11. The method of claim 10 wherein said .beta.-adrenergic blocking agent is carvedilol, propranolol, metoprolol, timolol, oxprenolol or tertatolol.

12. The method of claim 9 wherein said IFN-.gamma. is administered in combination with an antihypertensive drug.

13. The method of claim 9 wherein said IFN-.gamma. is administered with an ACE-inhibitor.

14. The method of claim 9 wherein said IFN-.gamma. is administered with an endothelin receptor antagonist.

15. The method of claim 9 wherein said IFN-.gamma. is administered following the administration of a thrombolytic agent.

16. The method of claim 15 wherein said thrombolytic agent is recombinant human tissue plasminogen activator (rht-PA).

17. The method of claim 9 wherein said IFN-.gamma. is administered following primary angioplasty for the treatment of acute myocardial infarction.

18. A method for preventing or reducing an increase in the weight of heart of a patient at acute risk of developing cardiac hypertrophy, comprising administering to the patient an effective amount of interferon gamma (IFN-.gamma.).

19. The method of claim 18 wherein said patient has suffered myocardial infarction.

20. The method of claim 19 wherein said IFN-.gamma. administration is initiated within 48 hours following myocardial infarction.

21. The method of claim 20 wherein said IFN-.gamma. administration is initiated within 24 hours following myocardial infarction.

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PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Book

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#19	Search **congestive heart failure**	12:23:39	52129
#18	Search **#4 AND #17**	12:23:30	0
#17	Search **cardiac shunt**	12:23:23	55
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#7	Search **#4 AND #6**	12:18:07	14
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#3	Search **cardiovascular disease**	12:15:52	1091362
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spanning domains of the human HP4 receptor. The resulting PCR product is purified by agarose gel electrophoresis, cloned into an expression plasmid such as pGEX (Pharmacia, Piscataway, N.J.) and used to transform *E. coli* by standard procedures. The positive clones are identified and induced to express the fusion protein, which is purified by well known methods.

The purified fusion protein is injected into the breast muscle of chickens (50–100 μg/injection) with booster injections given at two week intervals. The IgY antibodies are purified from the egg yolks by well known methods and their specificity determined by immunoblotting of tissue extracts.

In addition, monoclonal antibodies to the human HP4 receptor to can be prepared as discussed below.

EXAMPLE 8

Production of Monoclonal Antibodies Against the Human HP4 Receptor

The HP4 receptor-transfected COS-7 cell lysate, isolated as described in Example 7, is centrifuged to isolate membranes. The isolated membranes are injected in Freund's complete adjuvant into mice. After 9 booster injections over a three week period, the spleens are removed and resuspended in PBS. The resuspended spleen cells are mixed (approximately 4:1) with SP2/0 myeloma cells. Polyethylene glycol is added to fuse the myeloma and spleen cells, and the hybridomas are selected in HAT medium. The fused cells are aliquoted to allow growth of only one cell in each well of a 96 well microtiter plate. Each cell is expanded, the media removed and secreted proteins are labeled with ^{125}I. The labeled media from each well is used to probe a Western blot of transfected and untransfected COS-7 cell membranes.

The desired hybridoma produces a monoclonal antibody that strongly binds a protein band in a transfected COS-7 cell membrane lane on a Western blot, but does not bind to any other protein in that lane or in an untransfected COS-7 cell membrane lane (control). This method can be used to detect those cells expressing the human HP4 receptor.

EXAMPLE 9

Production of Stably-transfected Cells

To produce CHO cells stably transfected with the human HP4 gene, CHO cells are cotransfected with 10–30 μg human HP4 and 1–5 μg pSV2Neo carrying the neomycin resistance gene by calcium phosphate precipitation (Graham and Van der Eb, (1973) Virology, 52: 456–467). The cells are then subjected to selection with 600 μg/ml genetecin (G418; Gibco). The resistant colonies are selected, expanded and screened for receptor expression using $[^3H]$-PGE_2 binding as described in Example 3.

A murine homolog of the human HP4 prostaglandin receptor gene is isolated as described below.

EXAMPLE 10

Isolation of a Murine HP4 Prostaglandin Receptor Gene

The HP4 gene, isolated as described in Example 1, is digested with restriction enzymes by well-known methods to obtain a DNA segment of approximately 1–1.5 kilobases. This segment is nick-translated using a kit (Gibco BRL, Gaithersburg, Md.) and $[^{32}P]$-dATP, then used to screen mouse cDNA libraries which are available from several commercial sources including Clontech (Palo Alto, Calif.). The positive clones are sequenced and aligned with the HP4 sequence using one of a number of computer sequence alignment programs well-known in the art to determine whether the mouse clone shares significant sequence identity with human HP4

EXAMPLE 11

Antisense Oligonucleotides Directed to Human HP4 Prostaglandin Receptor

Antisense agents directed to human HP4 prostaglandin receptor mRNA may used to attenuate the effects of endogenous HP4 receptor agonists in patients having conditions including, without limitation, chronic asthma or immunosuppression. Such antisense agents include oligonucleotides that comprise "native" deoxyribonucleotides, or that may comprise modified nucleotides. Modified nucleotides are monomeric compounds not usually (or ever) found in nature which have the ability to form hydrogen-bonded base pairs with a nucleotide base and are further able to be heteropolymerized into a linear oligonucleotide or oligonucleotide analog. Examples of modified bases include, for example, 2'methoxyribonucleotides, methylphosphonate nucleotides, and phosphorothioate nucleotides. Additionally, antisense agents may comprise oligonucleotide analogs such as peptide nucleic acids (PNAs); for the purpose of this application, PNAs and similar oligonucleotide analogs shall be considered to consist of modified nucleotides. Numerous additional modified nucleotides exist and are known to the person of skill in the art; such additional modified nucleotides are intended to fall within the scope of this term. As used herein, the term "oligonucleotide" shall include oligonucleotide analogs such as those mentioned above, and shall mean a short linear molecule having the ability to form hydrogen bonds with the nucleotide bases of a specific segment of a single stranded nucleic acid molecule. Depending upon the specific type of modification, modified antisense agents may be more resistant to nuclease digestion, may have a greater melting temperature as (T_m), and/or a greater mRNA specificity than oligonucleotides made of unmodified nucleotides. These properties can result in an increased ability to prevent expression of a target protein. The antisense agents described herein function to bind HP4 receptor DNA and/or mRNA and to prevent transcription or translation by any of a number of mechanisms such as the recruitment of RNase H activity to a DNA:RNA hybrid with subsequent destruction of the RNA or through steric hindrance by the antisense agent of ribosome access to the 5' translation initiation region of the target gene.

Antisense oligonucleotides may be delivered to the target cell as the "naked" oligonucleotide by injection, infusion, or inhalation into the target tissue. However (particularly in the case of charged antisense agents) entry of the antisense agents into the cell through the apolar portions of the cell membrane can be problematic, and can result in a decrease in delivery and effectiveness. To overcome this problem, alternative delivery strategies have been devised.

One such strategy involves encasing the antisense agent in a liposome. Liposomes are artificial membrane analogs composed of lipids having polar headgroups. Particularly preferred for negatively charged antisense agents are liposomes containing cationic lipids, which function to neutralize the charge of the antisense agent and are attracted by the negatively charged outer plasma membrane. Additionally, liposomes may contain other types of lipids such as sterols

-continued

Phe Ala Val Cys Ser Leu Pro Phe Thr Ile P he Ala Tyr Met Asn Glu
275 280 285

Thr Ser Ser Arg Lys Glu Lys Trp Asp Leu G ln Ala Leu Arg Phe Leu
290 295 300

Ser Ile Asn Ser Ile Ile Asp Pro Trp Val P he Ala Ile Leu Arg Pro
305 310 315 320

Pro Val Leu Arg Leu Met Arg Ser Val Leu C ys Cys Arg Ile Ser Leu
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L30	6391311 and l10	0	L30
L29	l6 and L27	60	L29
L28	l10 and L27	94	L28
L27	congestive adj heart adj failure	4281	L27
L26	l10 and L25	1	L26
L25	cardiac adj shunt	13	L25
L24	l10 and L23	2	L24
L23	valvular adj regurgitation	37	L23
L22	l10 and L21	20	L22
L21	aortic adj stenosis	242	L21
L20	l10 and L19	1	L20
L19	renhui.in. and yang.in.	4	L19
L18	l10 and l15	1	L18
L17	l10 and l14	1	L17
L16	l8 and L15	3	L16
L15	nicholas.in. and paoni.in.	21	L15
L14	hsienwie.in. and lu.in.	1	L14
L13	hsienwie.in. and lu.in.L12	0	L13
L12	hsienwie.in. and needham.in.	0	L12
L11	l8 and L10	1	L11
L10	l6 or L9	5382	L10
L9	ifn	3842	L9
L8	hongkui.in. and jin.in.	4	L8
L7	l4 and L6	6	L7
L6	interferon adj gamma	3042	L6
L5	L4 and ifn	7	L5
L4	cardiac adj hypertrophy	513	L4
L3	ifn and cardiac hypertrophy	52	L3
L2	4727138 and cardiac hypertrophy	1	L2
L1	4727138	49	L1